

REMARKS

The present Amendment responds to the Office Action dated February 28, 2006. The Examiner set a shortened statutory period of three (3) months to respond, making the present Amendment due by May 28, 2006. Accordingly, filed concurrently herewith is a petition for a three (3) month extension of time so that the present Amendment is timely if filed by August 28 2006.

In the Office Action, claims 1-55 were pending, with claims 14-22, 25, 33 and 51-55 withdrawn from consideration as being drawn to a non-elected invention pursuant to 37 CFR § 1.142(b). The Examiner has rejected claims the examined claims under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 112, second paragraph. The examined claims have also been rejected under 35 U.S.C. § 102(b) as being anticipated by the 1997 Zheng et al. article entitled "Characterization of mitochondrial cytochrome b gene from *Venturia inaequalis*" (hereinafter referred to as the Zheng et al. article). Additionally, the Examiner has rejected the examined claims under 35 U.S.C. § 103(a) as being unpatentable over the Zheng et al. article in combination with one or more of the following references: the 1998 Landegren article in *Genome Research* (hereinafter the Landegren reference), U.S. Patent No. 6,326,145 to Whitcombe et al., and the 1998 Corran et al. article in *Pesticide Science* (hereinafter the Corran et al. reference). Further, in the Office Action, the Examiner has provisionally rejected claims 1-13, 23, 24, 34-36, 44-46, and 47-50 under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over various claims in copending US Application No. 10/483,979.

Without conceding the Examiner's position with respect to any of the claim rejections, Applicants have chosen to cancel all 55 claims and replace them with new claims 56-60. Applicants submit that each of the new claims find proper support in the specification and address each of the Examiner's rejections. Specifically, new independent claim 56 finds support in original claim 11 and in the application as originally filed, for example, on page 3 (lines 6-23), page 6 (lines 5-6, 14-16, and 28-31), page 10 (lines 6-7 and Table 2), page 11 lines 2-18, page 42 (lines 21-29) and in the Examples. New dependent claim 57 is supported in the application as filed, for example, at lines 14-16 on page 6. New dependent claim 58 is supported, for example, in the specification at lines 9-10 on page 9. Claim 59 finds basis in the specification, for example, on page 7, lines 8-11 as well as at lines 23-24 of page 9. Finally, dependent claim 60 finds support in the application as originally filed, for example, on page 11, lines 2-9.

Although the rejected claims have been cancelled, Applicants have addressed below each of the Examiner's rejections in the Office Action in the order in which they appear. For the sake of

clarity, Applicants have provided section headings, which correspond to the numbers of the rejections as they appear in the Office Action.

Item 3: Rejection of claims 1-13, 23, 24, and 34-50 under 35 U.S.C. § 112, first paragraph.

Taking each rejection in turn, the Examiner has taken the position that the specification is enabling for “an amino acid change of a glycine to alanine at the 143 codon”, but “does not reasonably provide enablement for any mutation in a fungal nucleic acid that gives rise to any strobilurin analogue or other compound in the same cross resistance group in a mitochondrial gene.” (OA p. 3). Again, while not conceding the Examiner’s position in this regard, the subject matter of new independent claim 56 relates to the detection of resistance caused an amino acid change of a glycine to alanine at the 143 codon.

The Examiner appears to also take the position that the specification is only enabling with respect to the detection of resistance that is observed at a G to C mutation in the second base-pair of the codon. However, Applicants respectfully submit that the specification is clearly enabling for mutations in for example, the third position of the codon. The Examiner’s attention is directed to Table 1 on page 9 in conjunction with line 23 page 9 to line 1 page 10 of the specification. Here, one of ordinary skill in the art is provided with the sequence of the region of wild-type (non-mutant) cytochrome *b* which encodes the codon corresponding to codon 143 in *S. cerevisiae* for a number of different plant pathogenic fungi, in Table 3. This information when coupled to knowledge of the degeneracy of the genetic code as described in Table 1 and pages 9-10, easily enables the ordinarily skilled person to design suitable primers for detecting a mutation occurring at both positions 2 and 3.

Additionally, new independent claim 56 claims the fungicide to which the stated mutation confers resistance. Since the strobilurin analogues have a single site mode of action (see lines 4-10 on page 2 and the references cited therein) it follows that should the G143A mutation be detected in a plant pathogenic fungus, the mutation will confer resistance to all the stated fungicides.

Item 4: Rejection of claims 1-13, 23, 24, and 34-50 under 35 U.S.C. § 112, first paragraph.

Here, the Examiner takes the position that “the written description requirement has not been satisfied for the claims as they are broadly written.” (OA, p. 14). Specifically, the Examiner asserts that the specification does not convey that “applicants were in possession of a representative number of mutations within the broadly claimed genus of mutations in a fungal nucleic acid where

the presence of said mutation in a mitochondrial gene results in fungal resistance to strobilurin analogs or compounds in the same cross resistance group." (OA p. 13-14). Presently, the subject matter of the new claims presented in the application relate to the specific gene of a fungal phytopathogen that is mutated (i.e. cytochrome *b*) and also to the specific region within that gene wherein the mutation lies (i.e. the codon that corresponds to codon 143 in the *S. cerevisiae* cytochrome *b* gene sequence).

Item 5: Rejection of claims 1, 5-7, 10, 13, 23, 24, 34, 36-39, 41, 44, 47-50 under 35 U.S.C. § 112, second paragraph.

Here, the Examiner rejected the claims as indefinite first for including language in parentheses such as "...any (or a) single nucleotide polymorphism technique...", as well as for containing the term "around". Applicants note that none of the new claims presented herein contain language in parentheses or the term "around".

Item 6: Rejection of claims 1, 2, 5-8, 10, 11, 34, 35, 44, and 45 under 35 U.S.C. § 102(b).

Applicants submit that the new independent claim 56, as well as its dependent claims, is not anticipated by the Zheng et al. article. The Zheng et al. article describes the characterization of the mitochondrial cytochrome *b* gene from the plant pathogen *Venturia inaequalis*. The gene was characterised through sequencing. The gene that was sequenced was isolated from a fungal isolate rated as sensitive to strobilurin fungicides (see materials and methods). Analysis of the amino acid sequence encoded by the gene revealed that there were no mutations present at the positions that had been shown to confer resistance to strobilurins in *S. cerevisiae* or strobilurin producing fungi (see final sentence under "Amino-acid sequence of cytochrome b" on page 364 and also Table 1 on page 364).

Accordingly, the Zheng et al. article merely teaches a non-mutated wild-type nucleotide sequence for cytochrome *b* in a plant pathogen that is sensitive to strobilurin fungicides. Since no mutations were found in the *V. inaequalis* cytochrome *b* gene, the Zheng et al. article clearly does not describe a method of detecting resistance or sensitivity in a fungal phytopathogen, wherein the resistance is caused by the mutation as claimed in new claim 56. Furthermore, the Zheng et al. article relies on sequencing and not on PCR-based methodology as claimed in claim 56 to detect a mutation (if any) in the cytochrome *b* gene. Accordingly, claim 56, as well as its dependent claims, is not anticipated by the Zheng et al. article.

Item 7: Rejection of claims 3, 4, 9, 12, 13, 36-39, 46, 47, 49, and 50 under 35 U.S.C. § 103(a).

Applicants submit that new claims 56-60 are not obvious in view of the combined teachings of the Zheng et al. and Landegren articles. The subject matter of the new claims relates to the identification that a mutation leading to the G143A substitution in cytochrome *b*, out of all of the potential cytochrome *b* gene mutations which could occur, is the resistance determinant with respect to strobilurin-type fungicides in phytopathogenic fungi in the field. Applicants assert that there is no suggestion in Zheng et al. that fungal plant pathogens are likely to contain mutations in their cytochrome *b* gene that could lead to strobilurin resistance. For example, in column 2 on page 365 of the Zheng et al. article, the paragraph beginning with "in contrast to all previous target sites..." the article specifically states that such mutations are deleterious to the fungus and impose a fitness penalty and it may thus be inferred that such mutations are unlikely to occur in plant pathogens.

Moreover, it is well-known that fungal resistance is not predictable. Rather, there are mechanisms other than target site alteration that lead to resistance. Accordingly it is not predictable a) that resistance to strobilurin type fungicides would occur in plant pathogens, b) what mechanism will be responsible for the resistance and c) if the mechanism occurs as an alteration to the target site, which particular residue within the target site will be altered. Indeed, on page 7 of the Office Action the Examiner has admitted that art of predicting mutations that result in strobilurin resistance is highly unpredictable.

There is thus no motivation in the prior art for the skilled man to use any method to look for the specific, G143A mutation in plant pathogens, let alone to use methods described in Landegren to look for this mutation: Particularly, one ordinary skilled in the art cannot predict which (if any) mutation will confer resistance. Indeed, the Zheng et al. article offers no guidance in this respect because the article does not teach the information required for to motivate one to consider whether SNP-based detection methods, such as those described by Landegren, might be suitable for detecting resistance if it were to occur. Accordingly, the method claimed in new claims 56-60 are not obvious over the Zheng et al. and Landegren articles.

Moreover, at the time at which the present patent application was filed, resistance of phytopathogenic fungi to strobilurin fungicides had not been detected. Thus it was not possible to predict whether strobilurin resistance would be observed in the field, let alone which (if any) would be the structural determinant in cytochrome *b* that would be responsible for such resistance. Accordingly, it was a great surprise and entirely unpredictable that when Applicants sequenced the cytochrome *b* gene of isolates from the first three strobilurin resistant isolates of phytopathogenic

fungi – *Erysiphe graminis*, *Sphaerotheca fulginea* and *Plasmopora viticola*, which are genetically diverse phytopathogens - the only mutation that was observed led to a replacement of the amino acid glycine with the amino acid alanine at position 143 in the encoded protein. This observation could not have been predicted, and certainly was not suggested, by the references made of record.

Thus the inventive step underlying the present invention as claimed is in the recognition that it is the G143A mutation above any other putative mutation in cytochrome *b* that gives rise to the high levels of resistance to strobilurin type fungicides in the phytopathogenic fungi in the field. It is only when the skilled man is in possession of this information (which he was not prior to filing of the present patent application) that he can rely on the nature of the mutation, which is such that it could only arise from a single nucleotide mutation in the second base of the triplet encoding the amino acid at position 143, to devise the simple, rapid, accurate and sensitive PCR based assays of the invention which are capable of detecting the presence of resistant isolates of phytopathogenic fungi in mixed samples isolated from the field."

Items 8 and 9: Rejection of claims 23, 24, 48 and 40-43 under 35 U.S.C. § 103(a).

These claims have been rejected under 35 U.S.C. § 103(a) as being obvious over the Zheng et al. article in view of the Whitcombe et al. patent, or in further view of the Corran et al. reference. Applicants submit that both of these rejections have been rendered moot by the deletion of claims 23, 24, 48 and 40-43.

Items 10 and 11: Provisional Double Patenting Rejection of claims 1-6, 9-13, 23, 24, 34-36, 44-50.

Applicants respectfully submit that the Examiner's provisional double patenting rejection based on the claims in co-pending Application Serial No. 10/483,979 has been overcome by the new claims in this amendment. Particularly, the subject matter of the new claims relates to the G143A mutation while the identified claims of the co-pending application 10/483,979 relate to methods for detecting strobilurin resistance wherein the resistance is caused by a F129L mutation (not G143A).

Based upon the foregoing, Applicants submit that the pending claims are in condition for allowance and the Examiner is courteously solicited to pass this application on to allowance. No other fees are believed to be payable at this time. However, the Commissioner is authorized to debit any applicable fees from the deposit account of the undersigned, No. 50-1676 in the name of Syngenta Crop Protection, Inc.

Respectfully submitted,

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